
Guidance for Industry

Submitting and Reviewing Complete Responses to Clinical Holds

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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User Fees
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This guidance represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

Under Food and Drug Administration (FDA) regulations, an investigational new drug application (IND) is either allowed to proceed or placed on clinical hold (21 CFR 312.42). A clinical hold is an order issued by the FDA to the applicant to delay a proposed clinical investigation or to suspend an ongoing investigation. A clinical hold may be designated either a *complete clinical hold* or a *partial clinical hold*. An applicant may respond to a clinical hold. Once the applicant has submitted a complete response to the clinical hold, the Agency must evaluate the response and decide whether to lift the hold. The Agency has committed itself to respond to the applicant within 30 days. This guidance is intended to describe how applicants should submit responses to clinical holds so that they may be identified as complete responses and the Agency can track the time to response.

We have provided a glossary at the end of this guidance to ensure that key terms are used consistently.

II. BACKGROUND

Section 117(3)(c) of the Food and Drug Administration Modernization Act of 1997 (Modernization Act) provides that "any written request to the Secretary from the applicant of an investigation that a

¹This guidance has been prepared by the Review Management Working Group comprising individuals from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. (OMB control number 0910-0445)

On June 1, 1998, the President instructed all Federal agencies to ensure the use of plain language in all new documents. This guidance reflects Agency efforts to comply with the President's plain language initiative.

clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor [sic], within 30 days after receipt of such request."² In addition, in conjunction with the reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA), the Agency committed to user fee performance goals incorporating the same response time. In her letter to Congress regarding reauthorization of PDUFA, the Secretary of Health and Human Services endorsed the Agency's commitment to respond to an applicant's complete response to a clinical hold within 30 calendar days of the Agency's receipt of the applicant's complete response. Beginning in fiscal year (FY) 1998, the Agency committed to respond to at least 75 percent of complete responses within 30 calendar days of receipt of the complete response. In fiscal years 1999-2002, the Agency's goal is to respond to at least 90 percent of the complete responses within 30 calendar days of receipt of the complete response.

To implement section 505(i)(3)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) and the PDUFA goals, in the *Federal Register* of December 14, 1998, FDA amended its IND regulations to state that the Agency will respond in writing to a sponsor's request that a clinical hold be removed from an investigation within 30 calendar days of the Agency's receipt of the request and the sponsor's complete response to the issues that led to the clinical hold (21 CFR 312.42(e)).

III. POLICIES AND PROCEDURES

The regulations in 21 CFR 312.42(c) require that when FDA concludes there may be grounds for imposing a clinical hold, FDA will "attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order." FDA experience is that most potential holds, particularly those based on inadequate patient monitoring, can be resolved through such discussion. However, if FDA determines that a study must be placed on clinical hold, it becomes subject to section 505(i)(3) of the Act.

A. What happens when the Agency imposes a clinical hold?

The Agency communicates the clinical hold to the sponsor, usually in a teleconference. After an IND has been placed on clinical hold, the study may not be initiated until the applicant has received a communication (via phone, fax, letter, or e-mail) from the Agency allowing the study to proceed (21 CFR 312.42(e)).

Within 30 days from the date of the teleconference placing an IND on clinical hold, the Agency must send the sponsor a clinical hold letter, signed by the Division Director or Acting Division Director, that describes in detail the reasons for the clinical hold (21 CFR 312.42(d)). The name of the responsible FDA contact will be included in the clinical hold letter.

² Section 117(3)(c) of the Modernization Act is codified in the Federal Food, Drug, and Cosmetic Act at 505(i)(3)(C).

The Agency may discuss additional nonhold issues regarding the IND in the clinical hold letter, or address them in a separate letter to the sponsor. If FDA addresses nonhold issues in the clinical hold letter, they should be in a separate section of the letter and be clearly marked as nonhold issues.

If the sponsor addresses all of the clinical hold issues identified in the Agency's clinical hold letter (a *complete response*), the Agency must respond to the sponsor within 30 days of receipt of the complete response (§ 312.42(e)). The 30-day response clock does not begin until a complete response to the clinical hold is received by the Agency.

B. How will the FDA measure the PDUFA goals on clinical holds?

The FDA will measure the PDUFA performance goals outlined in the Secretary's letter to Congress regarding Agency response to sponsors' complete responses to clinical holds based on commercial INDs.

C. How will the Agency handle clinical holds that were imposed prior to the publication of this guidance?

All clinical holds will be tracked for Modernization Act purposes and will be handled under the procedures described in this guidance, regardless of whether they were initiated before or after issuance of this guidance.

D. Can I address nonhold issues in my response to the Agency's clinical hold letter?

No, even if the Agency includes nonhold issues in the clinical hold letter, you should ensure that the complete response to a clinical hold letter contains *no material* related to issues other than the IND clinical hold. If you wish to address any nonhold issues raised by the Agency, please do so in a separate amendment or letter.

E. What else should I include in my response to the clinical hold letter?

If you believe you have responded to all of the issues raised in the clinical hold letter (i.e., that you are submitting a complete response), you should state this in the cover letter. Please type in large, bold letters at the top of the cover letter of the complete response: **CLINICAL HOLD COMPLETE RESPONSE**.

F. How should I send my response to ensure a timely review by the Agency?

You should send the complete response by a method that ensures that it has been received by the appropriate FDA document room. To facilitate a response to your submission, submit the

response in triplicate to the IND. You can ensure your submission is received and handled in a timely way by faxing a copy of the cover letter to the FDA contact listed in the clinical hold letter who is responsible for the IND.

G. What happens if I think my response is complete, but the FDA disagrees?

If FDA finds that your response is not complete, FDA will notify you as soon as possible by phone or other means of rapid communication, but no later than 30 days after receipt of your response. The Agency will tell you what information is needed to make it a complete response. The 30-day clock will not start until the FDA receives what it believes to be a complete response to the clinical hold letter.

H. How will the FDA handle an amendment providing additional information to the complete response that is submitted after the 30-day review clock has started? Will FDA extend the 30-day review clock?

No. Such an amendment received during the 30-day review process will not extend the clock. The division may choose to review the amendment in the time remaining, or stop the 30-day clock and start a new 30-day clock based on the receipt date of the amendment.

Amendments to the IND on nonclinical hold issues will be handled in the usual way.

I. What happens once the Agency receives the complete response?

The FDA will review your complete response within 30 calendar days after the receipt of a complete response, indicating whether the hold is lifted and, if not, specifying the reasons why not. After an IND has been placed on clinical hold, the study may not be initiated until the Agency has contacted you (via phone, fax, letter, or e-mail) telling you that the study may proceed (21 CFR 312.42(e)). (Communications by phone, fax, or e-mail will be followed by a letter.)

J. What happens if the Agency does not meet the 30-day response deadline?

As soon as possible after the review team determines that it will not meet the 30-day deadline, the Agency will telephone you and discuss the review progress to date and what is being done to facilitate completion of the review.

GLOSSARY

Agency's Response to an Applicant's Complete Response: A letter to the applicant from the Agency in response to an applicant's complete response in which the applicant (1) is allowed to proceed under the IND as proposed by the applicant (i.e., the clinical hold is lifted), (2) is allowed to proceed with specific restrictions not proposed by the applicant (i.e., a partial hold), or (3) is informed that studies under the IND may still not proceed. In the latter two cases, the letter will set forth why the clinical hold is being maintained. This letter should be issued to the applicant within 30 calendar days of receipt of the applicant's complete response.

Applicant's Complete Response to an IND Clinical Hold: A response from the applicant in which all clinical hold issues identified in the clinical hold letter have been addressed.

Clinical Hold: An order issued by FDA to the sponsor of an IND to delay or to suspend a clinical investigation for reasons described in 21 CFR 312.42. A *clinical hold* may be either a *complete clinical hold* or a *partial clinical hold*. A clinical hold (including a partial clinical hold) involves the Agency (1) requiring additional information and/or data, (2) reviewing the additional information and/or data, and (3) after the review, informing the sponsor that they can proceed. The Agency has *not* imposed a clinical hold if it requests additional information and/or data from the sponsor, but the sponsor does not have to wait for FDA review and authorization to proceed before initiating a new protocol.

- **Complete Clinical Hold:** A delay or suspension of all clinical work requested under an IND.
- **Partial Clinical Hold:** A delay or suspension of only part of the clinical work requested under the IND (e.g., a specific protocol or part of a protocol is not allowed to proceed; however, other protocols or parts of the protocol are allowed to proceed under the IND).

Commercial IND: An IND for which the sponsor is usually a corporate entity. Other INDs may be designated as commercial if it is clear the sponsor intends the product to be commercialized at a later date. INDs from the National Institutes of Health (NIH) will not be classified as commercial INDs until such time as the division determines that commercial development is being pursued.

30-day Response Clock: The FDA is required by the Modernization Act to respond in writing to the applicant within 30 calendar days after receipt of the applicant's complete response to a clinical hold (§ 312.42(e)).